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Accuracy of Human Circadian Entrainment under Natural Light Conditions: Model Simulations

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Abstract The patterns of light intensity to which humans expose their circadian pacemakers in daily life are very irregular and vary greatly from day to day. The circadian pacemaker can adjust to such irregular exposure patterns by daily phase shifts, such as summarized in a phase response curve. It is demonstrated in this paper on the basis of computer simulations applying actually recorded human light exposure patterns that the pacemaker can substantially improve its accuracy by an additional response to light. For that purpose, it should additionally change its angular velocity (and consequently its period τ) in response to light. Reductions of τ in response to light in the morning and increases of τ in response to light in the evening can lead to an increase in entrained pacemaker accuracy with about 25%. Circadian pacemakers have evolved as accurate internal representations of external time, and investigated diurnal mammals all seem to respond to light by changing the period of their circadian pacemaker (in addition to shifting phase). The authors suggest that also human circadian systems take advantage of this possibility and that their pacemakers respond to light by shifting phase and changing period. As a consequence of this postulated mechanism, the simulations demonstrate that the period of the pacemaker under normally entrained conditions is 24 h. The maximum accuracy corresponds to a day-to-day standard deviation of the time of phase 0 of circa 15 min. This is considerably more accurate than the light signal humans usually perceive.

Key words circadian system, light, twilight, zeitgeber, model, entrainment

By their behavior, humans expose themselves to very irregular daily light profiles. They withdraw in buildings for long time intervals and use artificial light. As a consequence, their circadian pacemaker receives highly variable light intensities as an input for entrainment. Since the human circadian pacemaker responds to light by shifting its phase (Honma and Honma, 1988; Zeisler et al., 1989; Minors et al., 1991), as summarized in phase response curves (PRCs), it will show daily advance and delay phase shifts in variable amounts. The purpose of this paper

is to demonstrate that the light intensity profiles humans expose themselves to lead to highly variable phase positions of their clocks when determined on the basis of classical phase response theory. It will be demonstrated that the accuracy of the pacemaker can be significantly improved by letting the period of the pacemaker respond to light as well.

In a recent publication (Beersma et al., 1999), we proposed a new view on entrainment of circadian pacemakers. At the heart of that work was the observation that the few diurnal species that have been

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investigated all showed both phase shifts and τ changes in response to a light stimulus. The potential importance of the τ changes for the accuracy of entrainment in diurnal mammals was investigated in a series of simulations. The model used for the simulations was as simple as possible. It was assumed that the state of the pacemaker at any moment was characterized by its momentary phase angle and by the instantaneous velocity with which it runs through its circadian cycle. In addition, it was assumed that the model pacemaker responds to light in two ways: (1) it changes its phase angle as characterized by a phase response curve (PRC) and (2) it changes its velocity as characterized by a τ response curve (τ RC). (Note: velocity and τ are inversely proportional because the velocity determines the time it takes to complete one revolution). It was further assumed that noise in the pacemaker system influences phase and period. In the simulations, the model pacemaker was exposed to a light-dark cycle. This was not the standard laboratory on-off light signal, but it was designed to reflect the natural light pattern at the equinox: At about half-hour intervals, the equinoctial clear sky intensity value was reduced by a random amount to simulate overcast and shades. In a series of simulations, the magnitude of phase shifts and τ changes in response to light were varied independently and systematically. It was shown that the accuracy of a pacemaker entrained by such quasi-natural light-dark cycles can benefit substantially from period control (τ changes) in addition to phase control. It was also observed that the period of the pacemaker in entrained situations was very close to 24 h for the majority of combinations of PRC magnitudes and τ RC magnitudes, including the combinations that yielded peak accuracy.

The simulations concerned model "animals," which were supposed to be continuously subjected to the light-dark cycle, such as is indeed the case for some animals in the wild (for instance, nonburrowing mammals). However, many species make burrows, nests, or houses in which they withdraw from the light for substantial fractions of the day. By this behavior, the light signal as it is perceived by their pacemakers becomes substantially different from the light-dark signal outdoors. Some nocturnally active burrowing species only see some twilight at dawn and/or dusk (Terman et al., 1991), while some diurnally active burrowing species never see the twilight and only experience darkness within their burrows (Hut et al., 1999). The human circadian pacemaker is also subjected to a light signal, which differs drastically from the light

outdoors. In daytime, we frequently withdraw from the natural light in buildings with varying window sizes. We use curtains to curtail the morning light and we increase the light level to which we expose ourselves by artificial light. From the work by Okada et al. (1983) and Savides et al. (1986), we know that the daily interval of light exposure beyond 1000 lux is often less than an hour. Cole et al. (1995) and Hébert et al. (1998) published average light exposure patterns of humans in winter and in summer. Although these papers clearly demonstrate substantial day-to-day variation, the information provided is insufficient to be used for simulations of pacemaker accuracy.

In this paper, we report on daily light exposure patterns of humans around the spring equinox and apply those patterns in simulations of the accuracy of the human circadian pacemaker to test whether the accuracy of the human circadian pacemaker would also benefit from τ responses in addition to phase responses. We conclude that minor velocity adjustments in response to light are sufficient to keep the human circadian system accurately entrained by highly erratic patterns of light exposure.

METHODS

Subjects and Light Recordings

Five healthy subjects (1 female, 4 males, age range 26-32 years) volunteered to participate in this experiment. They were all biology PhD students engaged in regular research activities. For 14-17 consecutive days centered around the spring equinox of 1999, each wore a light sensor (calibrated to record light intensity in lux) on their collars, which was connected to a portable data logger (Joblog, Bakker and Beersma, 1991). The experiment was performed in Groningen, the Netherlands, at a latitude of 53°10'N. Light intensity values were stored in memory at 1-min intervals. The sensitivity of the system ranged from 0 to 5075 lux with a resolution of 20 lux. Values beyond 5075 lux were attributed a value of 5075 lux. Technical problems resulted in the loss of 6 days of recording, 3 of which were compensated by a subject who continued wearing the sensor after 2 weeks.

Subjects listed events of which they suspected that light intensity as recorded would differ from light intensity at the level of the retina, such as sleep intervals. The effects of eye closure during indicated sleep intervals was accounted for by dividing measured

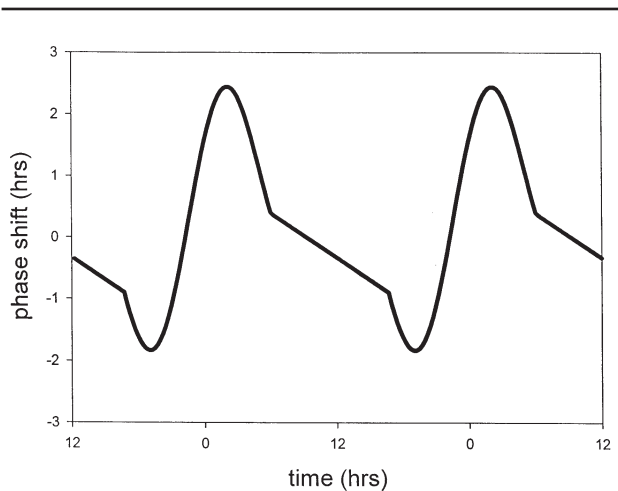


Figure 1. The phase response curve as derived from Honma and Honma (1988), Minors et al. (1991), and Jewett et al. (1997) that was applied in the simulations. The shifts apply to 3h light pulses of 3000lux light intensity.

light intensity by 30, as an estimate of eyelid light transmission.

The Model

The assumptions and structure of the entrainment model have been explicitly stated previously (Beersma et al., 1999). Briefly, the system is defined at each time by its instantaneous phase ϕ and velocity $1/\tau$. Both respond to light at a rate proportional to light intensity I . The responsiveness of the model system to light is defined on the basis of a PRC and a τ RC, the amplitudes of which are varied systematically in a series of simulations. The shapes of these response curves (Figure 1) are based on human PRC data obtained with single light pulses (Honma and Honma, 1988; Minors et al., 1991; see Beersma and Daan, 1993) and on Jewett et al.'s (1997) observations of a linear relationship between the timing of light pulses during the day and the resulting phase shift. First a smooth PRC was constructed by Fourier analysis of the single pulse data with three harmonics. The harmonic analysis resulted in a secondary peak and trough during the day, which is unrealistic as is shown by Jewett et al. (1997). This part of the curve was therefore replaced by a linear decline, the slope of which was estimated from Jewett et al.'s data.

In the absence of stimulation, a biological pacemaker will not be capable of maintaining its period exactly constant or its phase angle exactly proportional to time. We therefore incorporated small per-

turbations in the model. This was done by adding a random number (drawn from uniform distributions with zero mean) to τ at the end of each 4-min interval, and another random number to ϕ . Simultaneously, τ is reset to a new value to take into account the slow return of the pacemaker's velocity to its long-term stable value of $360/\tau_0$ during prolonged free-run in DD. In the model, this is realized by reducing the difference between τ and τ_0 by a contraction factor c . From mice data (Pittendrigh and Daan, 1976), c was estimated to be $0.99^{1/360}$. For humans, similar data are not available.

In summary, the model is described by the following two recursive equations, which are calculated every 4 min:

$$\phi_{i+1} = \phi_i + 24/\tau_i + \varepsilon_\phi + r_\phi \Delta\phi(\phi_i) \cdot I_i^{1/3} \quad (1)$$

$$\tau_{i+1} = \tau_i - c \cdot (\tau_i - \tau_0) + \varepsilon_\tau + r_\tau \Delta\phi(\phi_i) \cdot I_i^{1/3} \quad (2),$$

where

$\Delta\phi(\phi)$ = smoothed human PRC

r_ϕ = scaling factor for sensitivity to light in terms of phase shifts

r_τ = scaling factor for sensitivity to light in terms of τ changes

I_i = applied light intensity at time t

c = rate of contraction of τ to τ_0

τ_0 = long-term steady-state value of τ in DD

ε_ϕ , ε_τ = random numbers, drawn from rectangular distributions of zero mean and width = η_ϕ , η_τ

In this model a realistic equinoxial light-dark cycle is applied with fluctuating light intensity, I_e , as measured during 14 successive days in 1 individual. We use the cubic root value of light intensity to account for the light sensitivity characteristics of the human visual system (Stevens, 1961; Kronauer, 1990). Calculations were based on 1000 days. For each day, 1 of the 14 light profiles was selected randomly.

The behavior of the model system was investigated for various combinations of the PRC and τ RC amplitudes, r_ϕ and r_τ . The output variable under study is the accuracy of the pacemaker system. For that purpose, the standard deviation of the clock times at which the phase angle equals zero is calculated. The accuracy of the pacemaker system is defined as the reciprocal value of this standard deviation in hours and has the dimension h^{-1} . In each simulation, the standard devia-

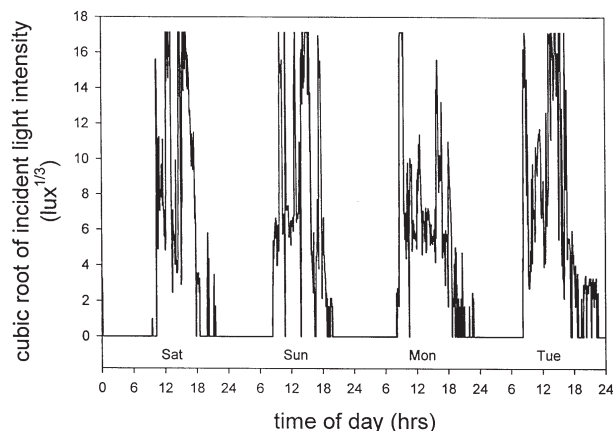


Figure 2 Example of 4 days of light exposure, recording of 1 human subject. Temporal resolution is 4min. Intensity resolution is 20lux. Maximum detection level is 5075lux.

tion, and hence accuracy, is computed over 1000 days of the model system, after skipping the initial 100 days to allow for transients to disappear. τ_0 was set to 24.2 h (Czeisler et al., 1995; Beersma and Hiddinga, 1998).

RESULTS

Human Light Exposure

Examples of light exposure recordings of a single subject are presented in Figure 2. Since the intensity response curve of the human circadian pacemaker fits closely to a cubic root function (Kronauer, 1990; Boivin et al., 1996), cubic root values of the observed intensities were taken. The amount of time spent in light intensities over 1000 lux shows considerable day-to-day variation, as does the timing of these events. On average, the subjects spent 99 min in light intensities over 1000 lux (range: 0–312 min; average daily duration of outdoors light intensity above 1000 lux: 614 min). Obviously, the light signal to which the human circadian pacemaker entrains is extremely irregular and variable from day to day.

In total, we collected 67 recordings of complete days, recorded by 5 subjects. The average daily profile over all recordings is shown in Figure 3. As expected from literature data, resulting values are always below 1000 lux. Interestingly, the average light exposure pattern is rather asymmetrical with a steep rise in the morning and a shoulder in the evening. The morn-

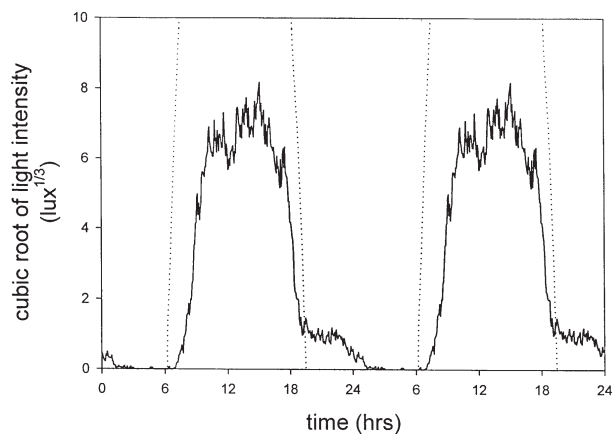


Figure 3 Average cubic root light profile recorded in 67 days around the spring equinox at 52° Northern latitude. Five subjects contributed to these results. Dotted lines indicate light intensities from the sky.

ing rise was between 8 and 9, much later than civil twilight and must be behaviorally determined. The evening shoulder reflects artificial lighting. Obviously, truncation both at the upper and lower end of the light intensity scale affects the precise location of the average curve.

Impact of Realistic Light Exposure on the Human Circadian Pacemaker

Recorded light exposure values of 1 subject were used for simulations of pacemaker accuracy. In a series of simulations, PRC amplitude was varied from 0 to 2 in steps of 0.05 (2 meaning that the amplitude was twice as large as the one that was presented in Fig. 1). Each value of PRC amplitude was combined with a series of τ RC amplitudes (0.1 meaning that the change in τ in hours corresponding to the change in angular velocity was one-tenth of the phase shift in Fig. 1), to estimate pacemaker accuracy. The results are presented in Figure 4. The contour lines connect points with equal pacemaker accuracy. The results show that pacemaker accuracy is maximal near PRC strength = 0.15 and τ RC strength = 0.01. The maximal value is about 10 h^{-1} , which means that the minimal standard deviation of the clock times of phase = 0 is about 6 min. Before paying much attention to these results, we must first consider the possible impact of intrinsic pacemaker noise, which was not taken into account in the simulations of Figure 4 ($\epsilon_\phi = \epsilon_\tau = 0$).

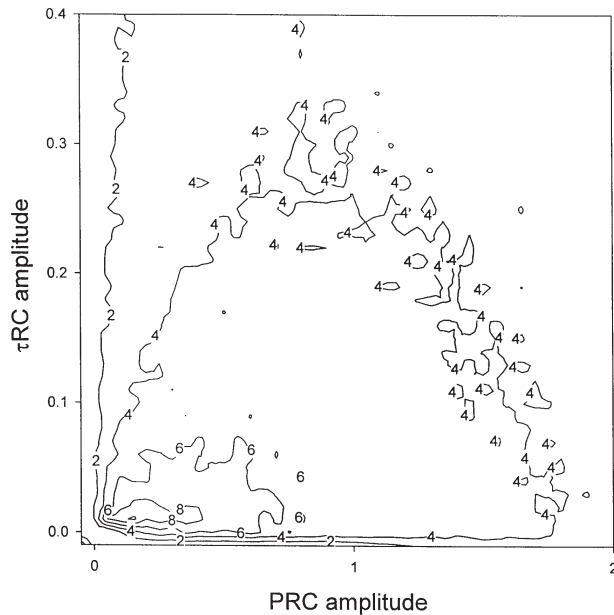


Figure 4 Simulations of pacemaker accuracy for a series of combinations of PRC strength and τ RC strength (see text). Lines connect points of equal accuracy. In these simulations, intrinsic pacemaker noise was set to zero. Light exposure data of a single subject were used.

Intrinsic Pacemaker Noise

The current state of our model pacemaker is determined by its momentary phase angle, ϕ_i , and by its instantaneous velocity, $1/\tau_i$. Somehow the values of ϕ_i and τ_i must be represented in the circadian system, otherwise a phase-dependent response could not be possible, and without some representation of τ , the system would not be able to sustain circadian oscillations. No matter how ϕ_i and τ_i are represented in the circadian system (concentrations of molecules, activity in a neural network, anatomic connectivity, etc.), their values must show some inherent fluctuations. These fluctuations we call noise. Noise must reduce pacemaker accuracy. As a result, pacemaker accuracy as determined in Figure 4 will not represent the actual situation: Pacemaker accuracy must be less. But how to estimate the intrinsic noise of the pacemaker?

To the best of our knowledge, this can only be done by making an additional assumption. Suppose that the human circadian pacemaker is optimally tuned to the light signal it is exposed to. In other words, suppose that it cannot improve its accuracy by changing its sensitivity to light. In that case, it can be argued that

the accuracy of the pacemaker due to the fluctuations in light exposure alone must be equal to the accuracy of the pacemaker due to its intrinsic noise alone. This is true because if, for instance, the accuracy of the pacemaker due to its own noise were better, the pacemaker would improve its final accuracy by reducing its sensitivity to light. By doing so, it would give preference to the better intrinsic accuracy. Hence, when we presume that the pacemaker is optimally tuned to the light signal, the accuracy of the pacemaker due to its intrinsic noise cannot be smaller than its accuracy due to the light fluctuations. By focussing on the impact of the fluctuations in the light signal, it can be similarly concluded that the accuracy of the pacemaker due to its intrinsic noise cannot be larger than its accuracy due to the light fluctuations either. Therefore, in the optimal situation, the two types of noise should have equal consequences for pacemaker accuracy. We further assume that the two are independent. The noise in the internal representation of pacemaker state is independent of the fluctuations in light exposure. The total variance of the times of phase = 0 is then the sum of the variance due to the light signal and the intrinsic variance. The two variances are assumed equal, so each represents half the final variance. The variance is proportional to the square of the standard deviation, hence, maximal pacemaker accuracy should be $1/\sqrt{2}$ times the maximal value without intrinsic noise. So the amount of intrinsic noise of the pacemaker should be such that the maximal accuracy reduces from about 10 h^{-1} to about 7 h^{-1} .

There is yet another problem to be solved. There are two sources of intrinsic noise, because there is noise in ϕ_i and there is noise in τ_i . Both the internal representation of phase and the internal representation of period must be fairly precise to be able to predict the occurrence of events that recur with circadian cyclicity. We do not see a way to a priori determine the relative impacts of these two sources of variance. As a simple guess, we have assumed that each source of noise independently reduces pacemaker accuracy by the same amount. Thus, in the absence of empirical estimates of the noise in ϕ_i and in τ_i we have set these at $\eta_\tau = 0.0015$ and $\eta_\phi = 0.000225$ to investigate the behavior of the system in the presence of noise. For the same subject under the influence of intrinsic pacemaker noise, maximum pacemaker accuracy reduces to 6 h^{-1} , observed at PRC strength = 0.4 and τ RC strength = 0.05.

With these values for the two types of noise in the model system, we simulated pacemaker accuracy for

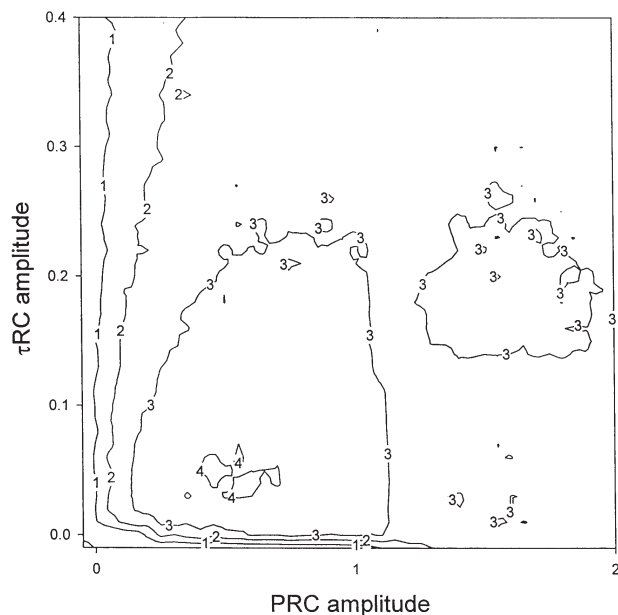


Figure 5 Simulations of pacemaker accuracy for a series of combinations of PRC strength and τ RC strength (see text). Lines connect points of equal accuracy. It was assumed that period and phase of the pacemaker were subjected to noise. The impact of these two sources of noise on pacemaker accuracy were made equal. The accuracy profile represents the average profile of 5 subjects.

all five subjects and calculated the average pattern (Fig. 5). Maximum pacemaker accuracy was about 4.2 h^{-1} and occurred at a PRC strength of 0.45 and a τ RC strength of 0.05. The average value of τ during the days of this simulation was 24.01 h. Clearly, the changes in τ that are due to the τ RC bring τ very close to 24 h. Maximum accuracy along the τ RC = 0 axis (according to classical PRC theory) is 3.3 h^{-1} at a PRC strength value of 0.75. Had the human pacemaker only responded to light by adjustment of period (PRC strength = 0), pacemaker accuracy would have been maximal at τ RC strength = 0.06 with an accuracy value of 1.2 h^{-1} .

DISCUSSION

Average equinoxial light exposure patterns as observed in this study show large similarity with winter and summer patterns reported by others (Cole et al., 1995; Hébert et al., 1998). Most important, all studies found highly variable light exposure patterns in humans, both within and between days. Since light is

the most important signal for the entrainment of the human circadian pacemaker, there is little doubt that the variability of the light signal must have an impact on pacemaker entrainment. The simulations in this study show that under certain assumptions about the magnitude of intrinsic pacemaker noise, maximal accuracy is reached near PRC strength = 0.5. This means that the pacemaker would be most accurate if the sensitivity of the pacemaker to light were less than is measured in Minors et al.'s (1991) and Honma and Honma's (1988) PRC. The large amplitude of the advance peak of the PRC in particular is due to one large value in the data of Honma and Honma (1988). Discarding this value would bring maximal pacemaker accuracy much closer to a point where PRC strength equals 1. A value of 1 would correspond to the situation that the actually measured PRC in humans is perfectly suited to obtain maximal pacemaker accuracy. Such reduction in PRC amplitude would also bring the curve closer to the linear slope obtained by Jewett et al. (1997) who described phase shifts in response to multiple light pulses applied in daytime.

It is not known from experimental investigations whether the human circadian pacemaker responds to light by changing τ . The simulations show that such response would improve pacemaker accuracy: A τ RC with an amplitude of about 0.05 times the PRC would improve pacemaker accuracy over the situation with no τ response by a factor of 1.25. The τ RC of this size would reach maximum responses of 6 min of shortening or lengthening to 3 h of light of 3000 lux at night or in the early morning, respectively. Maximum accuracy goes from 3.3 to 4.2 h^{-1} by including the τ response. Given that significant τ response curves have predominantly been observed in diurnal species, it is not unlikely that humans have developed a similar response characteristic but that this has hitherto been overlooked in phase shift experiments.

In comparison to many other biological processes, circadian pacemakers are extremely precise: The standard deviation is in the order of a few promille of their period (Pittendrigh and Daan, 1976; Daan, 1987). The development of such high precision must have been triggered by natural selection to serve important biological functions. If the precision of the pacemaker is important, it seems likely that the gain achieved by additionally changing the period of the pacemaker in response to light is actually exploited. Therefore, we predict that the human circadian pacemaker responds to light by both shifting its phase and adjusting its

period. By doing so, the period of the pacemaker under normal conditions will (on average) almost equal 24 h (see also Beersma et al., 1999). Subsequently, phase shifts of the pacemaker in response to light are only required to retain proper phase, no longer to compensate for a difference between pacemaker period and imposed period. As a result, the pacemaker need not be so sensitive to the light, by which it is also less sensitive to the erratic fluctuations of light intensity. That is the reason why the simulations reveal higher accuracy when τ responses are included.

The maximum accuracy that resulted from the simulations is about 4 h^{-1} . This corresponds to a standard deviation of the times at which circadian phase 0 occurs of 15 min. If the model is a good representation of the human circadian pacemaker, this means that under normal light-dark conditions, day-to-day fluctuations in the timing of phase = 0 have a standard deviation of 15 min. No experimental data are available to serve as a reference. Perhaps the most interesting comparison to make is the comparison with day-to-day fluctuations of dim light melatonin onset time (DLMO), as measured under continuous dim light conditions in humans (Gershengorn et al., 1998). In the absence of a light stimulus, this day-to-day variation amounts to $0.17 \text{ h} = 10 \text{ min}$. If we consider this to be due directly to the intrinsic noise of the pacemaker, we would expect the standard deviation to increase by a factor of $\sqrt{2}$ under the additional influence of light exposure. The value of 15 min is very close to the thus predicted value.

In summary, the simulations suggest that entrainment of the human circadian system like that of other diurnal mammals (Beersma et al., 1999) will involve both phase and period control for optimal accuracy. If this is true, the human system under conditions of daily life is expected to run at an endogenous period of exactly 24 h. This would solve the problem of how we can remain accurately entrained in the presence of highly inaccurate light signals.

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